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# **PCT**

### INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference C1-A0416Y1P	FOR FURTHER ACTION	See item 4 below	
International application No. PCT/JP2006/306800	International filing date (day/month/year) 31 March 2006 (31.03.2006)	Priority date (day/month/year) 31 March 2005 (31.03.2005)	
International Patent Classification (8t See relevant information in Form	h edition unless older edition indicated) PCT/ISA/237		
Applicant CHUGAI SEIYAKU KABUSHIKI K	AISHA		

1.	This international preliminary re International Searching Authorit	eport on patentability (Chapter I) is issued by the International Bureau on behalf of the ty under Rule 44 bis.1(a).
2.	This REPORT consists of a total	l of 6 sheets, including this cover sheet.
		ence to the written opinion of the International Searching Authority should be read as a reference report on patentability (Chapter I) instead.
3.	This report contains indications	relating to the following items:
	Box No. I	Basis of the report
	Box No. II	Priority
	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
	Box No. IV	Lack of unity of invention
ı	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
	Box No. VI	Certain documents cited
	Box No. VII	Certain defects in the international application
	Box No. VIII	Certain observations on the international application
4.		ommunicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but makes an express request under Article 23(2), before the expiration of 30 months from the priority

	Date of issuance of this report 03 October 2007 (03.10.2007)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Yoshiko Kuwahara
Facsimile No. +41 22 338 82 70	e-mail: pt07.pct@wipo.int

## PATENT COOPERATION TREATY

From the INTERN		AL SEARCHIN	G AUTHORI	ITY		•	ANSI
To:						P	CT TON
				9 -	INTER		PINION OF THE ARCHING AUTHORITY
				·		(PCT Ru	le 43 <i>bis</i> .1)
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		ent's file reference.	ie		FOR FURTI	ER ACTION See paragrap	h 2 below
		olication No. 2006/3068	300	International filing date (	  day/month/year		(day/month/year) 3.2005
Internati	onal Pat	ent Classification	(IPC) or both	national classification an	d IPC	· · · · · · · · · · · · · · · · · · ·	
			<u> </u>				·
Applica:		SEIYAKU	KABUSH	IIKI KAISHA			
1.	This o	pinion contains in	dications relat	ing to the following items	s:		****
	$\boxtimes$	Box No. I	Basis of the	opinion			
		Box No. II	Priority				
		Box No. III	Non-establis	shment of opinion with re	gard to novelty, i	wentive step and in	dustrial applicability
	Щ	Box No. IV	Lack of unit	y of invention			
		Box No. V		atement under Rule 43bis citations and explanation			tive step or industrial
	닏	Box No. VI	Certain docu	ments cited			
	片	Box No. VII	Certain defe	cts in the international app	plication		
	Ш	Box No. VIII	Certain obse	rvations on the internatio	nal application		
2.	FURT	HER ACTION					
	Interna than th	tional Preliminar is one to be the l	y Examining A iPEA and the	Authority ("IPEA") excep	of that this does not the International	ot apply where the	red to be a written opinion of the applicant chooses an Authority other le 66.1 <i>bis</i> (b) that written opinions of
	writter	reply together.	where approp		before the expi	ation of 3 months	nt is invited to submit to the IPEA a from the date of mailing of Form
	For fur	ther options, see	Form PCT/IS/	A/220.			
3.	For fur	ther details, see n	notes to Form I	РСТ/ISA/220.			
Name a	nd maili	ng address of the	ISA/JP	Date of completion	of this opinion	Authorized officer	
Facsimi	le No.					Telephone No.	

# WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2006/306800

Box	No. I Basis of this opinion	
ı.	With regard to the language, this opinion has been established on the basis of:	_
	the international application in the language in which it was filed	
	the translation of the international application into, which is the language of a	
	translation furnished for the purposes of international search (Rule 12.3(a) and 23.1(b)).	
2.	With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claime invention, this opinion has been established on the basis of:	d
	a. type of material	
	a sequence listing.	
	table(s) related to the sequence listing	
	b. format of material	
	on paper	
	in electronic form	
	c. time of filing/furnishing	
	contained in the international application as filed	
	filed together with the international application in electronic form	
	furnished subsequently to this Authority for the purposes of search	
	Thin said subsequently to this reductity for the purposes of scarcin	
3.	In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application a filed or does not go beyond the application as filed, as appropriate, were furnished.	
4.	Additional comments:	
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# WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2006/306800

Statement		pporting such statement	
Sideficia			
Novelty (N)	Claims	1-44	
	Claims		
Inventive step (IS)	Claims		Y
	Claims	1-44	<del></del>
Industrial applicability (IA)	Claims	1-44	
	Claims		
Citations and explanations:			
Document 1.		•	
		t of domain order on the activity of bacterially Fv antibodies., J. Mol. Biol., 2003, Vol. 330, No. 1,	
pages 99-111	,io cham	T v annocatos, g. Mol. Blon, 2003, von 530, 110. 1	
Document 2.		·	
		fic and bifunctional single chain recombinant	
•	g., 2001,	Vol. 18, No. 2, pages 31-40	
Document 3:	ino rata	rgeting of T cell effector function by recombinant	
		CD3 x anti-idiotype) induces long-term survival in the	
		, J. Immunol., 1998, Vol. 161, No. 3, pages 1454-1461	
Document 4:.	a moder.	, 3. Hillianot., 1996, vol. 101, 110. 3, pages 1434-1401	
•	al Cons	struction, expression, and activity of a bivalent	
		, J. Biol. Chem., 1994, Vol. 269, No. 1, pages 199-206	
Document 5:		, , <sub>1</sub> , <sub>1</sub>	
MACK M. et al., A sma	ll bispec	ific antibody construct expressed as a functional	
		tumor cell cytotoxicity., Proc. Natl. Acad. Sci. USA.,	
1995, Vol. 92, No. 15, p			
Document 6.			
		eutic approach for thrombocytopenia by minibody	
	oietin red	ceptor., Blood, 15 January 2005, Vol. 105, No. 2, pages	
562-566		*	
(Continued in suppleme	ntal box	)	
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# WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/JP2006/306800

Supplemental Box

In case the space in any of the preceding boxes is not sufficient. Continuation of:  $\texttt{Box} \ \ \texttt{V.2}$ 

•Claims 1, 2, 5, 6, 8, 9-12, 14-17, and 19-22

Documents 1-3 state that incorrect Fv combinations occur in bispecific sc(Fv)2 antibodies.

Documents 1-3 do not mention the intention to eliminate bispecific sc(Fv)2 antibodies formed by erroneous combinations of such VH and VL fragments (hereinafter, "erroneous bispecific sc(Fv)2"). However, this authority finds that persons skilled in the art will naturally recall that such an "erroneous bispecific sc(Fv)2" antibody will lose its original antigen binding capability and should not be present together with the original "bispecific sc(Fv)2."

This being the case, this authority finds that persons skilled in the art can easily conceive of trying to eliminate such "erroneous bispecific sc(Fv)2" antibodies by performing an affinity purification procedure using a bispecific antigen corresponding to the original "bispecific sc(Fv)2" as described in document 4. In addition, this authority finds that persons skilled in the art can attempt to use a substance purified thereby as a pharmaceutical composition and the like in accordance with the properties thereof as needed.

In this context, judging from the statements in the DESCRIPTION of this application, bispecific substances are included in the scope of the terms "sc(Fv)2," "single chain diabody," and "bivalent scFv" in the claims, and because the aforementioned original "bispecific sc(Fv)2" and the "erroneous bispecific sc(Fv)2" are related as "structural isomers" referred to in the DESCRIPTION of this application, this authority finds that essentially performing the aforementioned affinity purification procedure corresponds to the step wherein structural isomers in an sc(Fv)2 composition are separated, and a specific structural isomer is acquired.

In addition, this authority finds that no particularly outstanding effect is provided by adopting the constituent elements of the inventions of the above claims.

As a result, this authority finds that persons skilled in the art could easily arrive at the inventions of the above claims based on the descriptions in documents 1-4, and therefore these inventions lack an inventive step.

#### •Claims 3, 4, 7, 13, and 39-43

Document 1 states that when the linker connecting two scFv fragments is long, for example 15 amino acids or longer, the likelihood that the antibody will become an "erroneous bispecific sc(Fv)2" is increased by the flexibility of that linker. In addition, documents 5 and 6 specifically describe linkers comprising 15 amino acids. (Continued in supplemental box)

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2006/306800

Supplemental Box

V. 2

In this context, this authority finds that persons skilled in the art familiar with these descriptions will naturally recall adjusting the linker length so that a desired bispecific sc(Fv)2 will be formed as much as possible.

In addition, this authority finds that no particularly outstanding effect is provided by adopting the constituent elements of the inventions of the above claims.

As a result, this authority finds that persons skilled in the art could easily arrive at the inventions of the above claims based on the descriptions in documents 1-6, and therefore these inventions lack an inventive step.

#### •Claims 18 and 44

Figure 1A of document 3 shows that an original "bispecific sc(Fv)2" and "erroneous bispecific sc(Fv)2) are detected as different bands in an SDS-PAGE procedure.

This being the case, this authority finds that persons skilled in the art will naturally recall attempting separation based on the differences in physical properties between original "bispecific sc(Fv)2" and "erroneous bispecific sc(Fv)2" antibodies. In addition, this authority finds that persons skilled in the art can attempt to discover structural differences therein from the enzymatic degradation products thereof and the like as needed.

In addition, this authority finds that no particularly outstanding effect is provided by adopting the constituent elements of the inventions of the above claims.

As a result, this authority finds that persons skilled in the art could easily arrive at the inventions of the above claims based on the descriptions in documents 1-4, and therefore these inventions lack an inventive step.

#### •Claims 23-38

Performing substitutions and the like in part of the amino acid sequence of a mutually interacting protein and changing the mode of mutual interaction thereby was widely known technology to persons skilled in the art before the priority date of this application.

In this context, this authority finds that the structure of the variable region of the antibody was investigated in detail before the priority date of this application, and based on that knowledge, persons skilled in the art could perform amino acid substitutions as needed such that as few "erroneous bispecific sc(Fv)2" antibodies as possible will be formed.

In addition, this authority finds that no particularly outstanding effect is provided by adopting the constituent elements of the inventions of the above claims.

As a result, this authority finds that persons skilled in the art could easily arrive at the inventions of the above claims based on the descriptions in documents 1-6, and therefore these inventions lack an inventive step.